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## Vitamin E may significantly increase and decrease mortality in some population groups : [Comment]

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## **Vitamin E may significantly increase and decrease mortality in some population groups**

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### **Comment on:**

Meta-Regression Analyses, Meta-Analyses, and Trial Sequential Analyses of the Effects of Supplementation with Beta-Carotene, Vitamin A, and Vitamin E Singly or in Different Combinations on All-Cause Mortality: Do We Have Evidence for Lack of Harm?

Bjelakovic G, Nikolova D, Gluud C.

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**Hemilä H.**

Vitamin E may significantly increase and decrease mortality in some population groups  
[Posted by hemila on 27 Oct 2013 at 10:07 GMT]

**PLoS ONE**

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In their meta-analysis, Bjelakovic et al. calculated that vitamin E in doses above the RDA (>15 mg) may slightly increase mortality by 3% (95% CI: 0% to 5%)(1). This estimate was based on the pooling of the results of 44 studies. However, study-level analyses can lead to different conclusions than do corresponding individual-level analysis, a difference which is called the “ecological fallacy” (2).

We analyzed the heterogeneity in vitamin E effect on the mortality of ATBC Study participants, who were Finnish male smokers aged 50-69 years at baseline. The combination of age and dietary vitamin C intake modified the effect of 50 mg of vitamin E supplementation (3). The evidence for heterogeneity over 6 subgroups was very strong (chi-square [5 df] = 22.2, P = 0.0005).

In 11,448 ATBC Study participants aged 50-62 years who had dietary vitamin C intake above the median, vitamin E increased all-cause mortality by 19% (95% CI: 5% to 35%), whereas in 872 participants aged 66-69 years who had vitamin C intake above the median, vitamin E decreased mortality by 41% (95% CI: -56% to -21%)(3). Vitamin E did not influence mortality among men who had vitamin C intake below the median. The modifying effect of vitamin C was not explained by other substances in fruit and vegetables (3). At the biochemical level, the interaction between vitamins C and E is well known (4) and may explain the role of vitamin C as a modifying factor.

In the younger ATBC participants (50-62 y), vitamin E started to increase mortality only after 3.3 years so that there was no effect on mortality during the first 3.3 years (95% CI: -18% to +19%), but mortality was 38% (95% CI: 17%, 63%) higher in vitamin E group thereafter (3). Adding the second vitamin E effect improved the regression model significantly (chi-square [1 df] = 7.1, P = 0.007) and therefore the supplementation-time modification is not easily explained by chance. Thus, in addition to age and dietary vitamin C intake, the effect of vitamin E depended also on the duration of its supplementation. The delay in the harm may be explained by its fat solubility.

Furthermore, the benefit of vitamin E for men aged 66 and over implies that the survival time might be influenced. In a further exploratory analysis, we found that those administered vitamin E lived half a year longer at the upper end of the survival curves (5).

The strong evidence of heterogeneity in the vitamin E effect has important implications. There is no justification to search for a “single universal effect of vitamin E on mortality” which is assumed to be valid for all persons on the globe, such as the average increase of 3% calculated by Bjelakovic et al. (1). The confidence intervals of the older ATBC Study men (n = 872), and the confidence intervals of the younger men (n = 11,448) after 3.3 year supplementation, are both strongly inconsistent with a 3% universal effect of vitamin E in doses above the RDA.

There is very strong evidence that the vitamin E effect on pneumonia is also heterogeneous over the 29,133 males of the ATBC Study (6,7). Although pneumonia is not a common cause of mortality in the ATBC Study participants, this heterogeneity gives further support to the notion that various biological effects of vitamin E may be heterogeneous over the population, at least among Finnish men. We should not assume that heterogeneity in Finnish men implies heterogeneity in all other people, but heterogeneity in Finnish men refutes the concept that there is a “universal same size effect among all people” such as the +3% effect calculated by Bjelakovic et al. (1).

In 2009, I criticized the Cochrane review on antioxidants and mortality which is a predecessor of the PLoS ONE meta-analysis (1). Bjelakovic et al. replied to my criticisms and my criticism and their replies are both available in the revised 2012 version of the Cochrane review (8). I do not consider that all their replies are satisfactory and therefore I repeat here a major comment, since the problem is also valid for the new meta-analysis (1).

In 2009, I wrote that Bjelakovic et al. ignored the evidence indicating that vitamin E effect is not uniform over the population. They ignore the heterogeneity found in the ATBC Study also in the new meta-analysis (1). Now Bjelakovic et al. write that “Our meta-analyses had little trial heterogeneity. This further increases the trustworthiness of our findings” (1). This kind of reasoning is not valid when an individual-level analysis has shown very strong evidence that there is

heterogeneity within one large trial (3,5). When individual-level analysis and study-level analysis find different results, we should put more weight on the individual-level analysis, and we should suspect that the study-level analysis may suffer from the ecological bias (2).

Small studies have wide confidence intervals and therefore they are unlikely to generate heterogeneity, even if the biological effect might be variable between population groups. Large studies include people who substantially vary by age and other characteristics. If there is heterogeneity within a large trial, the possible harms and benefits may be largely cancelled when calculating the average effect, as is the case in the ATBC Study. For such reasons, little trial heterogeneity in a study-level analysis does not necessarily tell anything about the potential variations between populations groups. Individual-level analyses are much more crucial (2).

Given the mainly negative findings in the antioxidant trials (1,8), it seems justified to discourage the general population from taking supplements until we have better knowledge of the groups of people who may benefit.

However, a single vitamin E effect estimate, such as +3%, does not apply to all people over the globe since, at least, a substantial proportion of Finnish men in the ATBC study are inconsistent with such an effect. The individual-level analysis of the ATBC Study suggests that trials on vitamins E and C for men older than 70 years are warranted (3,5).

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